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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/942,310	08/29/2001	Carl Risinger	524592001900	7722

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EXAMINER	
JOHANNSEN, DIANA B	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/942,310	RISINGER ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003 and 16 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 9-16* is/are pending in the application.

4a) Of the above claim(s) *10-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0801; 0503*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the Response to Species Election filed July 15, 2003 and the complete listing of claims filed December 16, 2003. Claims 1 and 9-16 are currently pending in the application. It is further noted that the paper and computer readable forms of the Sequence Listing filed August 29, 2001 have been entered.

Election/Restriction

2. Applicant's election of the combination of polymorphic positions 36, 194, and 942 of SEQ ID NO: 2 in the Response to Species Election filed July 15, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1 and 9 read on the elected species, and are now under consideration. It is again noted that upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141.

3. Claims 10-16, as well as claim 1 in part, as drawn to combinations of polymorphic positions other than the elected combination set forth above, are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the Response of July 15, 2003.

Priority

4. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the United Kingdom on August 30, 2000. It is noted, however, that applicant has not filed a certified copy of the British application as required by 35 U.S.C. 119(b).

Information Disclosure Statement

5. Regarding the IDS filed August 29, 2001, it is noted that the examiner has completed the citation for document "AN" (see handwritten correction). Applicant is requested to review and acknowledge the correction.

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, e.g., page 3). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

7. The use of the trademarks TAQMAN, EXPEDITE, GENEAMP, QIAAMP, and GENBANK has been noted in this application. Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 9 are indefinite because it is not clear whether the claims are drawn to a method "for determining a human's capacity to metabolize a substrate of a CYP2D6 enzyme," as recited in the preamble of claim 1, or to a method of detecting "at least three polymorphisms" in a gene region or regions, as recited in the final process step of the claim. The language of the claim does not make clear how the detection of polymorphisms relates to or allows one to determine "capacity to metabolize a substrate," and it is unclear as to what steps are actually required to carry out the claimed method (i.e., does the claim actually require a step of determining capacity to metabolize a substrate?).

Claims 1 and 9 are indefinite over the recitation of the limitations "said region" and "the region" in claim 1, because there is insufficient antecedent basis for these limitations in the claims. While claim 1 previously recites "regions of CYP2D6 genes," the claim does not previously refer to a particular "region."

Claims 1 and 9 are indefinite over the recitation of the language "said region is represented by a sequence as set forth in SEQ ID NO: 2." It is unclear as to what relationships between a region and SEQ ID NO: 2 would be encompassed by this language, and whether this language actually requires isolation of nucleic acids comprising or consisting of SEQ ID NO: 2, or whether the claims may encompass other

molecules containing regions that are in some way "represented by" SEQ ID NO: 2. As this terminology is vague and indefinite, it is not clear what types of molecules are actually embraced by the claims.

Claims 1 and 9 are indefinite over the recitation of the language "polymorphic sites represented by positions _____ of SEQ ID NO: 2." It is unclear as to whether this language actually requires the presence of SEQ ID NO: 2, or whether the claims also encompass, e.g., portions of SEQ ID NO: 2, or molecules "represented" in some way by SEQ ID NO: 2. To the extent that the claims may not actually require SEQ ID NO: 2, it is not clear what polymorphic sites are actually encompassed by the claims; i.e., how would one identify a site or sites "represented by" positions in SEQ ID NO: 2 if SEQ ID NO: 2 itself is not present? Clarification is required.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Raimundo et al (European Journal of Clinical Pharmacology 55:A5 [1999]).

It is first noted that the instant claims as written merely require steps of isolating single stranded nucleic acids and detecting polymorphisms in a region encoded thereby; the claims do not include a method step in which "a human's capacity to metabolize a substrate of a CYP2D6 enzyme" is actually determined. As Raimundo et al disclose method steps meeting the requirements of the claims, Raimundo et al anticipate the claimed invention. Further, it appears that "determining a human's capacity to metabolize a substrate of a CYP2D6 enzyme" merely constitutes a previously unrecognized benefit of performing the method of Raimundo et al.

Raimundo et al disclose direct sequencing of a PCR fragment encoding 5' flanking sequences of CYP2D6 that are "represented by" the sequence described by Applicant as SEQ ID NO: 2; Raimundo et al thereby disclose a step meeting the requirements of Applicants' step "a)" (see entire abstract). Raimundo et al further disclose detecting the nucleotides present at positions –590, -1338, and –1496 of their CYP2D6 molecules, which positions correspond to nucleotides 36, 194, and 942 of Applicants' SEQ ID NO: 2 (see, e.g., Table 2 of the disclosure, which specifies the relationships between positions in Applicants' SEQ ID NO: 2 and the known numbering system for the CYP2D6 gene)(see entire abstract of Raimundo et al). Raimundo et al thereby anticipate the claimed invention.

12. Claims 1 and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by Raimundo et al (Pharmacogenetics 10:577-581 [10/2000]; hereinafter referred to as "Raimundo et al-2").

Raimundo et al-2 disclose direct sequencing of a PCR fragment encoding 5' flanking sequences of CYP2D6 that are "represented by" the sequence described by Applicant as SEQ ID NO: 2; Raimundo et al-2 thereby disclose a step meeting the requirements of Applicants' step "a)" (see entire reference, particularly page 578 – "Materials and Methods" section). Raimundo et al-2 further disclose detecting the nucleotides present at positions –590, -1338, and –1496 of their CYP2D6 molecules, which positions correspond to nucleotides 36, 194, and 942 of Applicants' SEQ ID NO: 2 (see, e.g., Table 2 of the disclosure, which specifies the relationships between positions in Applicants' SEQ ID NO: 2 and the known numbering system for the CYP2D6 gene)(see entire Raimundo et al-2 reference, particularly the abstract and page 579, right column). Accordingly, Raimundo et al-2 anticipate the claimed invention. While it is again noted that the claims as written do not actually require a method step in which "a human's capacity to metabolize a substrate of a CYP2D6 enzyme" is actually determined, Raimundo et al-2 further disclose that different nucleotides that may be present at position –1496 of the CYP2D6 gene are associated with different drug metabolism phenotypes (see entire reference, particularly Figure 1, page 579, right column, and page 580).

13. Claims 1 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Epidauros Biotechnologie AG [WO 01/55432 A2 [8/2/01; international filing date 1/30/01]; hereinafter referred to as "EB").

EB discloses direct sequencing of a PCR fragment encoding 5' flanking sequences of CYP2D6 that are "represented by" the sequence described by Applicant

as SEQ ID NO: 2; EB thereby disclose a step meeting the requirements of Applicants' step "a)" (see entire reference, particularly pages 18-22 and the CYP2D6 upstream flanking sequence of Figure 1). It is noted that the CYP2D6 upstream sequences sequenced by EB include the positions corresponding to nucleotides 36, 194, and 942 of Applicants' SEQ ID NO: 2 (see Figure 1 of EB, noting that the nucleotides described by EB as –1584, -1426, and –678 correspond to nucleotides 36, 194, and 942, respectively, of instant SEQ ID NO: 2). Accordingly, EB anticipates the claimed invention. While it is again noted that the claims as written do not actually require a method step in which "a human's capacity to metabolize a substrate of a CYP2D6 enzyme" is actually determined, EB further discloses that a C to G polymorphism at their position –1584 of the CYP2D6 gene (which corresponds to position 36 of instant SEQ ID NO: 2) is "strongly associated with lower metabolic rates (i.e. higher enzyme activity in vivo)" in individuals with the *2 allele of CYP2D6 (see page 20), and further state that "Detection of C or G at position –1584 bp in conjunction with identification of the *2/*0 genotype will therefore allow to make a quantitative prediction on the in vivo drug metabolism capacity" (see page 22).

14. Claims 1 and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by Epidauros Biotechnologie AG [WO 01/55432 A2 [8/2/01]).

EB discloses direct sequencing of a PCR fragment encoding 5' flanking sequences of CYP2D6 that are "represented by" the sequence described by Applicant as SEQ ID NO: 2; EB thereby disclose a step meeting the requirements of Applicants' step "a)" (see entire reference, particularly pages 18-22 and the CYP2D6 upstream

flanking sequence of Figure 1). It is noted that the CYP2D6 upstream sequences sequenced by EB include the positions corresponding to nucleotides 36, 194, and 942 of Applicants' SEQ ID NO: 2 (see Figure 1 of EB, noting that the nucleotides described by EB as –1584, -1426, and –678 correspond to nucleotides 36, 194, and 942, respectively, of instant SEQ ID NO: 2). Accordingly, EB anticipates the claimed invention. While it is again noted that the claims as written do not actually require a method step in which "a human's capacity to metabolize a substrate of a CYP2D6 enzyme" is actually determined, EB further discloses that a C to G polymorphism at their position –1584 of the CYP2D6 gene (which corresponds to position 36 of instant SEQ ID NO: 2) is "strongly associated with lower metabolic rates (i.e. higher enzyme activity in vivo)" in individuals with the *2 allele of CYP2D6 (see page 20), and further state that "Detection of C or G at position –1584 bp in conjunction with identification of the *2/*0 genotype will therefore allow to make a quantitative prediction on the in vivo drug metabolism capacity" (see page 22).

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Diana B. Johannsen
February 29, 2004